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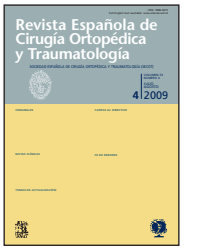

REVIEW ARTICLE

Osteoarthritis as a genetic condition

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Abstract
Osteoarthritis is an example of a complex disease, which arises from the interaction of genetic and environmental factors. In this paper we review the different types of studies that can be conducted in order to analyze the contribution of genetic factors to the pathogenesis of complex diseases as well as the genes whose polymorphisms have been associated to the risk of developing osteoarthritis.
The significant benefits that surgery can offer patients with advanced-stage osteoarthritis beg the question of whether there genetic studies are really of any use. The answer is clearly in the affirmative. On the one hand, an awareness of the genetic factors involved in the onset and development of osteoarthritis may help identify and control subgroups of individuals who are at a higher risk at an early stage. Furthermore, identification of the genes involves could help discover new therapeutic targets that may lead to effectively halting the process, which is something we cannot do with our patients at present.

PALABRAS CLAVE
Artrosis;
Genética;
Estudios de asociación;
Polimorfismos

La artrosis como enfermedad genética

Resumen
La artrosis es un ejemplo de enfermedad compleja, que se origina por la interacción de factores genéticos y ambientales. En este trabajo revisamos los diferentes tipos de estudios que permiten analizar la contribución de los factores genéticos a la patogenia de las enfermedades complejas y los genes cuyos polimorfismos se han relacionado con el riesgo de desarrollar artrosis.

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Dado el importante beneficio que aporta la cirugía a los pacientes con artrosis avanzada, cabría plantearse si estos estudios genéticos tienen realmente alguna utilidad. La respuesta es claramente afirmativa. Por un lado, el conocimiento de los factores genéticos implicados en la aparición y el desarrollo de la artrosis puede permitir identificar y controlar subgrupos de individuos de mayor riesgo en fases precoces. Por otro lado, la identificación de los genes involucrados puede llevar a determinar nuevas dianas terapéuticas que permitan frenar de manera eficaz el desarrollo del proceso, algo que no podemos ofrecer a nuestros pacientes en la actualidad.

Introduction

Osteoarthritis is an example of a complex disease that results from the interaction of acquired factors with a hereditary predisposition, which is determined by multiple genes. Although numerous genetic association and linkage studies have been carried out in recent years, none of them has succeeded in clearly establishing which genes are really responsible for the said hereditary predisposition. Nonetheless, substantial evidence is available that some of the genes involved are those related with the Wnt pathway and the synthesis of prostaglandins.

Given the significant benefits contributed by surgery to patients with advanced osteoarthritis, the reader may wonder whether these genetic studies are indeed of any use. The answer is clearly in the affirmative. On the one hand, understanding on the genetic factors involved in the onset and development of osteoarthritis could make it possible to identify and control subgroups of high risk individuals at earlier phases. Moreover, identification of the genes involved could assist in identifying new treatment targets that may help arrest de development of the arthritis process, which is something we cannot at present offer to our patients.

The purpose of this review article is to analyze the relationship between osteoarthritis and genetics.

Hereditary, acquired and complex diseases

Traditional descriptions of the origins of diseases classified them into "hereditary" and "acquired". The former were characterized by being genetically passed on to descendants, by generally manifesting themselves early in life and by the lack of an effective treatment to combat them. Some examples from the realm of skeletal pathology include osteogenesis imperfecta, mucopolysaccharidosis and ochronosis. Acquired diseases for their part were caused by external agents (eg. infections, trauma) or by endogenous disorders provoked by causes that are not always well-understood, could appear at any age and were not genetically transmitted by parents to their offspring. Nevertheless, in the last few decades these concepts have changed as it became known that many of the so-called "acquired" diseases also include a strong hereditary component. Thus, at present these disorders have come to be called "complex diseases" as they are understood to be the result of an interaction between genetic and environmental factors. Unlike classical hereditary conditions, the genetic component in these conditions does not depend on the alteration of a single gene, but rather on the modification of several genes, which turns them into "polygenic" hereditary diseases. A good proportion of the most prevalent chronic diseases in our environment fall within this category, including disorders as frequent as arteriosclerosis, diabetes, obesity, osteoporosis and osteoarthritis. The purpose of this study is to offer a brief review of the existing data on the genetic component of osteoarthritis and place it within the general context of the genetics of complex diseases in order to provide lay readers who are not experts in this kind of study with a better grasp of this complex issue.

Mutations and polymorphisms

The hereditary component of complex diseases explains why, when confronted to similar external stimuli, some individuals go on to develop the disease whereas others do not. For example, even if agricultural work is a known risk factor for the development of hip arthritis[1], it is evident that not all agricultural workers are afflicted with coxarthritis. Genetic variability among individuals is the basis for such differences in susceptibility. In this connection, human genome sequencing has made it possible to ascertain that the human genome contains several "polymorphic" areas, i.e. areas that differ across individuals. These variants are called "polymorphisms" and can be of different types. The most common are the following:

- Single nucleotide polymorphisms (SNPs): these are single-base differences, i.e. points in the DNA sequence where some individuals have, for example, an adenine (A) and others a guanine (G). These polymorphisms are sometimes called "biallelic", since in general there are only 2 possible forms in the population. SNPs are highly frequent; on average one of these polymorphic areas occurs for every 300 nucleotides. Since the human genome has some 3,000 million nucleotides, the total number of SNPs is estimated at around 10 million. Some of them are located in coding areas of DNA but others can be found in regions with no known function (fig. 1).
- Repeat polymorphisms: these are sequences of nucleotides that occur repeatedly, with the number of repetitions varying across individuals. The best known repeat polymorphisms are microsatellites, where

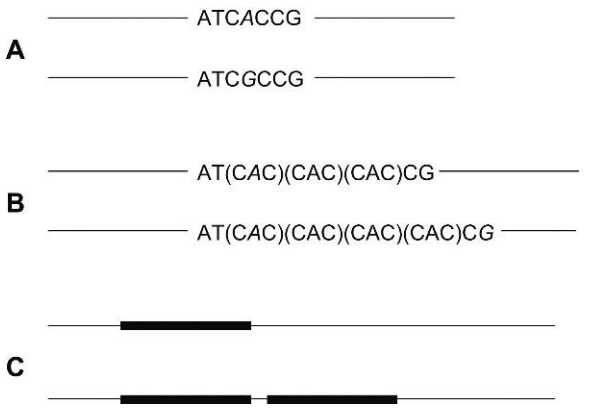

Figure 1 Examples of polymorphisms. A: A/G single-nucleotide polymorphism. B: Repeat polymorphism with a variable number of CAC triplets. C: Copy number polymorphisms, with a vast DNA segment, comprised of thousands of nucleotides (represented by the thick line), duplicated in some individuals.

repetitions are constituted by groupings of just a few nucleotides (between 2 and 6). These polymorphisms are mostly located in non protein-coding regions.

— Copy number polymorphisms: some individuals have a different number of copies of specific DNA segments, made up of thousands or millions of nucleotides. What often happens is that in some individuals such segments are duplicated; on other occasions, there are insertions, deletions or other complex changes. It is estimated that 12% of the human genome can present with these types of variations, for which reason copy number polymorphisms, even if they have been scarcely studied, are thought to be involved in a good deal of human variability.

Polymorphisms are DNA variations that are fairly common among the population. By definition, the least frequent variant must occur in at least 1% of individuals. Some of them have functional consequences, either because they are located in coding regions and they modify the aminoacid sequence of the protein coded by the gene, or because they are located in regulating regions that influence the expression of the gene (i.e. the rate at which DNA is transcribed into RNA, which will in turn govern protein synthesis) or some other mechanism. Apart from these "functional" polymorphisms, there are "non functional" polymorphisms, which are neutral, i.e. they have no known consequences. At any rate, functional polymorphisms in general have limited effects. This means that the fact that one variant should be present rather than another may influence cell activity, but not to a great extent. In other words, they cannot by themselves cause disease. In this connection, polymorphisms must be distinguished from "mutations". Mutations are also changes in the DNA that occur in some individuals but, unlike polymorphisms, these changes have significant functional repercussions on cell biology and can trigger the onset of a disease. Therefore, mutations and polymorphisms are variants of DNA that can be transmitted from parents to their children, but while the former are infrequent and cause the classical hereditary diseases, the latter are frequent and participate in the pathogenesis of complex diseases.

Types of studies on the genetic origin of complex diseases

There are different types of studies that can identify the genetic component of a complex disease.

— Family association studies. More often than not the first data about the genetic cause of a disorder come from observational studies that reveal that diseases tend to concentrate in family groups, so that patients report similar cases in their ascendants and descendants. In any event, it should not be forgotten that the grouping of cases in family groups is not synonymous with a hereditary origin since the members of a family do not only share genes, but often share other characteristics such as habits, place of residence, exposure to environmental factors and socio-economic status.

— Twin studies. Classical twin studies constitute an attempt to separate the contribution of hereditary factors from that of environmental factors in family associations. It is a known fact that monozygotic twins share a virtually identical DNA. On the other hand, dizygotic twins only share, on average, half of the alleles of the polymorphic regions of ADN. Therefore, when comparing the frequency with which the disease appears in pairs of monozygotic and dizygotic twins, we obtain an idea of the importance of genetic and environmental factors. In a disease highly influenced by the hereditary component, there will be many concordant pairs of monozygotic twins (i.e. pairs where both twins are healthy or both are sick); whereas among dizygotic twins the proportion of concordant pairs will be smaller and there will be a significant amount of cases where one of the twins is affected while the other is not. On the other hand, when the genetic component of the disease is less significant, the proportion of concordant pairs among monozygotic twins will be similar to that found among dizygotic twins. The hereditary component is often quantified by means of the "hereditability coefficient", which indicates what proportion of the risk of contracting a disease can be attributed to genetic factors.

— Linkage studies. The studies above can reveal that a certain condition has a genetic component to it, but they say nothing about which are the participating genes. The goal of linkage studies is to tackle this issue and identify the DNA region(s) that may be involved in the disorder. With that purpose in mind, several family generations are studied, with DNA being extracted from their members. Subsequently, a panel of (microsatellite or SNP) poymorphisms is analyzed. A large number of polymorphisms are studied. In the first few studies, just a few hundred were analyzed, but currently hundreds of thousands are used. These polymorphisms are distributed across the whole of the human genome and the fact that they may be functional or non-functional is irrelevant. They are selected simply as "markers" of a certain DNA region. Afterwards, an analysis is carried out to determine

whether the polymorphisms present in the parents are equally distributed among their children or whether, on the contrary, some alleles are more frequent in the diseased children than in the healthy ones. If that is the case, that DNA region would presumably be involved in the person's predisposition to the disease. It must be underscored that the polymorphism studied is not necessarily the direct cause of the disease. The cause may be that polymorphism or some other polymorphysm that lies in its vicinity since, as we know, DNA is transmitted from parents to children *en bloc*, namely, nearby regions in the DNA are transmitted together. Those regions constitute the so-called "haplotype blocks". Therefore linkage studies do not allow direct identification of the DNA variants involved in the disease, but they do "mark" the regions where these variants are to be found. A subsequent more detailed study will be necessary to identify the causing variants.

— Candidate gene studies. Schematically, these studies compare the frequency of the alleles of some polymorphisms in healthy and diseased individuals. Their design may either be population-based or case-control. In population-based studies, a genetic analysis is performed of a specific group within the general population and, at the same time, healthy and diseased individuals in the group are identified. In case-control studies, the first task is to identify a group of patients and then an analysis is made of healthy subjects of similar characteristics in terms of age, gender and other risk factors. The choice of the candidate genes, i.e. the genes whose polymorphisms are studied, is governed by several criteria. On some occasions, the selection comprises some of the genes present in the DNA regions that were previously associated to a risk to contract the disease by linkage studies. At other times, the choice is made on the basis of the knowledge available on the biology of the disease. For example, the genes related to the metabolism of carbodydrates are clear candidates in the case of studies on diabetes, whereas the genes involved in the metabolismo of the cartilage matrix are clear candidates in the case of osteoarthritis. Classical hereditary diseases can also assist in identify potential candidate genes, since the polymorphisms of the genes that mutate in those disorders may contribute to the development of associated complex diseases. For example, the lipoprotein receptor-related protein 5 (LRP5) is a receptor of Wnt, a peptide family that stimulates bone formation. A mutation of LRP5 has been identified that inhibits its effect and triggers a rare disease with bone and neurologic manifestations, the osteoporosis-pseudoglioma syndrome. The mutation, and hence the syndrome, are extremely infrequent. However, in the last few years it has been reported that some LRP5 polymorphisms that are frequent in the population, even if they cause fewer modifications to the function of the protein, influence on bone bass and on the predisposition to osteoporosis of the general population[2].

— Genomewide association studies (GWAS): In recent years the development of rapid genotyping techniques, and the use of chips in particular, has made it possible to carry out studies that simultaneously analyze the alleles of thousands of polymorphisms. These studies typically analyze a bery high number of SNPs, around 500,000, in healthy and diseased individuals to subsequently compare differences in the alleles in both groups. In this connection, these studies are similar to the candidate gene studies. However, genomewide association studies analyze polymorphisms distributed across all of the genome, without any previous selection of "candidates". Therefore they have the advantage of being able to identify genetic variants related to the disease through previously unknown pathways and mechanisms. Nevertheless, these studies are still costly, both because of the technology required and because of the need to analyze very large groups, made up of several thousand individuals, in order to possess enough statistical power to reliably identify the polymorphisms related to the disease.

Family association and twin studies in osteoarthritis

It is a well known fact that some patients develop osteoarthritis further to genetically acquired (ostechondrodysplasia, ochronosis, Wilson's disease, etc.) or environmentally acquired (infection, trauma, etc.) conditions. As regards cases of primary osteoarthritis, the disease is often triggered by a series of factors (repeated microtrauma, obesity, etc.) that act on individuals with a certain genetic predisposition. The existence of such a predisposition has been demonstrated by studies where patients with osteoarthritis report that their relatives also present with the disease. Thus, for example, it has been estimated that individuals whose relatives suffer from severe knee or hip osteoarthritis that resulted in implantation of a prosthesis are 2-5 times more likely to require a prosthetic replacement of the said joints than the general population[3,4]. The influence of heredity depends on the location of osteoarthritis. On the basis of twin studies, it has been estimated that the heritability component is a round 75% in the case of spondyloarthritis, 60% in hip arthritis, 40% in knee arthritis and 65% in hand arthritis[5]. Several studies have shown that the hereditary component is more significant in females than in males. Nonetheless, it remains to be shown whether this really reflects an interaction between genetic factors and other gender-related characteristics (hormone concentrations, etc.) or whether it depends on a greater variability of the exogenous factors in males, for example, regarding the different occupational activities. On the other hand, it should be considered that hereditary predisposition does not depend only on whether certain skeleton-related polymorphisms are inherited; rather, it encompasses elements related to both articular biology and to other associated organic characteristics associated in turn to the risk of contracting osteoarthritis, such as obesity.

Linkage studies in osteoarthritis

Different linkage studies have revealed the existence of some regions in the genome that are related to osteoarthritis.

Thus, it has been argued that hand osteoarthritis is associated to polymorphisms located in the long arm of chromosome 2 (regions 2q12-35), while hip arthritis has been associated to polymorphisms located in that same chromosome and in other regions of chromosomes 4, 6 and 16[3,5]. Nonetheless, these results have been scarcely reproducible and different studies have found linkage to different chromosome regions. In this, osteoarthritis is similar to other complex diseases, for which linkage studies have generally been of little use. In contrast to this, in monogenic or classical Mendelian hereditary diseases these types of studies have made it possible to identify the mutation causing the disease.

Candidate gene studies in osteoarthritis

Scientists have implicated the polymorphisms of many of the genes presumably involved in skeletal biology in the development of osteoarthritis. Ryder et al[6] recently conducted an exhaustive review of the studies published so far, so we will limit ourselves to citing just a few characteristic studies mentioned by different authors. In fact, as was the case with linkage studies, candidate gene studies are also quite often irreproducible.

This irreproduciblity could be attributed to several reasons. On some occasions, it is due to the fact that no real relationship exists between the polymorphism under study and the disease. In other words, to the fact that the relationship found by the initial study was merely incidental, i.e. there is no real relationship that can be replicated in subsequent studies. On other occasions, the apparent association between a polymorphism and the disease it not simply incidental, but rather it is influenced by population stratification phenomena. This happens when the study analyzes mixed populations, constituted by groups of different genetic history, characterized by varying risks to contract the disease. In this case, differences in allele frequency between healthy and diseased individuals are a result of the differences of the subgroups of different origin. But it is also important to consider that lack of reproducibility does not necessarily mean that there is no real relationship between the polymorphism and the disease. In fact, the influence of a certain polymorphism can manifest itself in some populations more than in others, depending on the differences that exist between them in terms of the exposure to environmental factors such as nutrition.

The following are some of the genes that have been related to osteoarthritis by several studies:

— Genes related to cartilage matrix constituents. These include collagen IX and XI, whose polymorphisms have been associated with spine arthritis. Aggrecan is a proteoglycan that contributes to the resistance of articular cartilage. Some of the polymorphisms of the *ACAN* gene, which codes for aggrecan's protein chain, have been related to the risk of developing hand arthritis.[6].
— Genes related to bone and cartilage metabolism. Estrogens play a key role in skeletal homeostasis and also seem to have a protective effect on cartilage[7,8]. Several studies have explored the relationship between the polymorphisms of the estrogen receptor gene and osteoarthritis, and different kinds of associations have been published between such polymorphisms and knee and hip arthritis[9,10,11,12]. It is also well-known that vitamin D regulates skeletal homeostasis and some studies have related the polymorphisms of the vitamin D receptor with knee and spine arthritis; however, not all authors have confirmed these findings[13]. The Wnt pathway play san important role in modulating the activity of bone cells, osteoblasts in particular[14]. It also seems to participate in the cartilage repair process that occurs in response to different deleterious stimuli[15]. The *FRZB* gene codes for a protein, the secreted frizzled related protein 3, which inhibits the activity of the Wnt pathway. Several studies have reported the existence of a relationship between certain polymorphisms of the *FRZB* gene and hip arthritis[16,17,18]. Moreover, the participation of this gene in the pathogenesis of osteoarthritis is borne out by the studies with knock-out mice where its expression was abolished. These mice, which do not express *FRZB*, develop alterations in the cartilage and periarticular bone similar to osteoarthritis in response to the damage induced by several chemical agents[19]. A recent study has shown that the polymorphisms of this gen can also influence the processes of osteolysis and heterotopic calcification that tend to ensue alter implantation of a hip replacement[20].
— Genes related with inflammation and cartilage degradation. Although less markedly than in other articular processes, osteoarthritis also contains an inflammatory component, which seems to be triggered by the remaining cartilage matrix. Several authors have published associations between the polymorphisms of certain genes of certain inflammation-related cytokines (such as interleukin-1 and its modulators) with knee arthritis. Asporin is an ill understood protein that, at least partly, influences cartilage metabolism since it inhibits the activity of the transforming growth factor TGFβ. Several studies have established a connection between certain polymorphisms of the asporin gen with the development of osteoarthritis. This influence seems to be greater in Asian than in Caucasian populations and to be more significant for knee than for hip arthritis[21]. Prostaglandins are also well-known modulators of the activities of bone cells and inflammation. The polymorphisms of the *PTGS2* gen, which codes for COX-2, an enzyme involved in prostaglandin synthesis, have been related with knee arthritis[22].

Genomewide association studies in osteoarthritis

Three genomic association studies have so far been published on osteoarthritis. One of them found an association between the *CALM1* gen, which codes for calmodulin, a protein related to intracellular calcium movements, and hip arthritis[23]. Nonetheless, the results obtained could not be reproduced in a subsequent study of British subjects. Conversely, Spector et al[24] reported an association between

LRCH1, a gene of unknown function, and knee arthritis, but the results could not be reproduced subsequently in studies carried out on Asian and British cohorts[25]. In a recent study, which typified some 500,000 SNPs in several European populations, a consistent relationship was found between knee arthritis and the polymorphisms in region q33 of chromosome 2, which houses the genes of 2 enzymes involved in prostaglandin synthesis, namely COX-2 and phospholipase[26].

Conclusions

From the above one can conclude that osteoarthritis undoubtedly incorporates a significant genetic component, which varies across the different locations where the disease manifests itself, but which can account for between one-third and three-quarters of the predisposition to contract the disease. Excluding patients with rare hereditary metabolic diseases, in the majority of cases the genetic component of osteoarthritis does not depend on a single gene, but rather on several. Thus, osteoarthritis is an example of a complex disease that results from the interaction of acquired factors with a hereditary predisposition determined by multiple genes. Although numerous linkage and association studies have recently been completed, none of them has succeeded in clearly establishing which genes are actually involved in the said hereditary predisposition. However, there is growing evidence of the involvement of some genes related to the Wnt pathway and with prostaglandin synthesis.

Given the significant benefits that surgery brings to patients with advanced osteoarthritis, the undertaking of genetic studies may be called into question. The answer is clearly in the affirmative. On the one hand, understanding the genetic factors implicated in the onset and development of osteoarthritis could help identify and control subgroups of individuals who are at a higher risk at an earlier stage. In addition, identification of the genes involved could lead to the identification of new therapeutic targets that may contribute to efficiently arresting the development of the arthritic process, an advantage we cannot as yet offer our patients.

Conflict of interests

The authors declare that they have no conflict of interests.

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